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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,883	09/19/2003	Chong-Sheng Yuan	466992001100	6779

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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,883	YUAN, CHONG-SHENG	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,21,22,31-34,37-42,44-48,50-55,58-65 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claims 1, 31, 39, 45, 50, 60 and 68, in the paper of 6/16/2010, is acknowledged. Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are still at issue and are present for examination.

Applicants' arguments filed on 6/16/2010 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Applicant's acknowledgment of the interview on 1/25/2010 is appreciated and noted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the rejection, applicants have amended claims 1, 31, 39, 45, 50, 60 and 68, and traverse the rejection as it applies to the newly amended claims.

Applicants continue their traversal in light of the amendments to the claims, and in view of the revised guidelines concerning compliance with the written description requirement.

Applicant's further note that they have amended the claim to recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. Applicants submit that the pending claims are limited structurally with respect to SEQ ID NO:2, and encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Applicants submit that the pending claims place numerical limitations upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2. Applciants submit this position on the basis that SEQ ID NO:2 is 356 amino acids in length and that changing one amino acid out of 356 amino acids results in a peptide having 99.72% sequence identity to SEQ ID NO:2. Applciants submit that a person of ordinary skill would easily be able to design such 99.72% identical polypeptides.

Applicants continue to note their previous comments regarding the knowledge and skills of a person of ordinary skill in the art relating to conservative amino acid substitutions, testing of conservatively substituted peptides, and the well-known structure-function correlation data for Hal2p that had been published at the time the application had been filed are incorporated herein in their entirety. It is noted that applicants submit Albert et al. to support their position of the available guidance in the art.

Applicants maintain that the pending claims are concordant with Example 11B of the written description guidelines, since the claims place structural limitations relevant to SEQ ID NO:2.

Applciants further submit that a person would be able to design and test derivative peptides for the requisite 90% activity since there is a recognized structure function relationship.

Finally applicants continue to submit that the protein of SEQ ID NO:2 was known in the art and a person of skill in the art would be able to correlate the structure of SEQ ID NO:2 with the requisite function, As discussed in Example 11B of the written description guidelines.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is found nonpersuasive for the reasons previously made of record and for those repeated herein.

Applicant's amendment of the claims to recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. While it is acknowledged that the pending claims are limited structurally with respect to SEQ ID NO:2 and "conservative substitutions, and encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2, the claims remain rejected because applicants have not placed any limitation upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2, nor have applciants adequately described that subgenus of mutations that retain 90% of the bisphosphate activity of SEQ ID NO:2. Thus applicants claimed chimeric proteins continues to comprise an enormous number of species, such that the disclosure of SEQ ID NO:2 is insufficient to adequately describe the claimed genus of variants of SEQ ID NO:2 having at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Given this lack of representative species, beyond SEQ ID NO:2, as encompassed by the full breadth of the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein having nucleotidase activity comprising the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for any chimeric protein having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising SEQ ID NO:2 having an unlimited number of conservative amino acid substitutions wherein the peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3 and methods of methods of their use, encompassed by these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. invention.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the rejection, applicants have amended claims 1, 31, 39, 45, 50, 60 and 68, and traverse the rejection as it applies to the newly amended claims.

Applicants continue to argue on the basis that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Applicants submit that experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance

regarding the direction of experimentation - time and difficulty are not determinative of undue experimentation if the experimentation is routine.

Applicants submit that in order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Applicants submit that in view of the amendments to the claims, Applicants submit that the claims meet the enablement requirement. The claims as amended recite that the second peptidyl fragment comprises SEQ ID NO:2 having one conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. As above, applciants submit that a chimeric polypeptide having one conservative amino acid substitution of SEQ ID NO:2 and wherein it retains at least 90% of the bisphosphate activity of SEQ ID NO:2 does not encompass those fragments having an unlimited number of conservative amino acid substitutions of SEQ ID NO:2 and thus it would not take an undue experimentation to arrive at this number of SEQ ID NO:2 mutants. Applciants submit that given this background, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of know biological activity was well settled and routine.

As above applciants submit that SEQ ID NO:2 is 356 amino acids in length and substituting one amino acid out of this 356 amino acid sequence would result in a

peptide having 99.72% sequence identity to SEQ ID NO:2. Applciants reference this in the context of the *Kubin* appeal drawn to a polypeptide which is 80% identical to amino acids 22-221 of SEQ ID NO:2. Applciants submit that one is far fewer than the roughly 40 around enabled by the Federal Circuit in *Kubin*.

As above this line of reasoning is acknowledged, but not found persuasive on the basis that while the claims are drawn to those polypeptide comprising SEQ ID NO:2 having one conservative amino acid substitution, this clearly reads on those having more than one conservative substitution. Thus applicants argued scope is not accurate and that argument dependent upon not found persuasive. Clearly a protein that has two, three or one hundred mutations is encompassed by a protein having one mutation.

Thus applicants argument regarding the person of skill in the art reading the specification and being able to design peptides having 99.72% sequence identity to SEQ ID NO:2 and test these polypeptides for the requisite activity is not specific to the size of the encompassed genus.

Applicants continue to submit that the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed. Applciants continue to submit that the specification expressly describes methods by which such polypeptides having conservative amino acid mutations can be prepared without any undue experimentation

and the art provides (i.e. Albert et al.) the crystal structure of Hal2p complexes with magnesium, lithium, AMP and Pi.

Thus, Applicants maintain that the specification provides reasonable guidance to the skilled artisan regarding how to make and use the invention, including providing sufficient guidance on protein structure and sufficient guidance on methods for designing variant proteins having a desired activity. Accordingly, Applicants respectfully submit that the present claims are fully enabled by the specification to overcome the rejection under 35 U.S.C. § 112, first paragraph.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

Applicants continue to argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the complete amino acid sequence of SEQ ID NO:2, and protocols for testing for biological activity of conservative substitutions of SEQ ID NO:2 are within the skill of the ordinary artisan. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., comprising conservative amino acid substitutions of SEQ ID NO:2) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. While applicants disclosure of SEQ ID NO:2 and means of testing for the claimed activity are known, it continues that applicants claims

are such that there is virtually no structural limitations required of the claimed variant of SEQ ID NO:2. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. Contrary to applciants arguments, the genus of those variants of SEQ ID NO:2 claimed is greater than 99.72% sequence identity to SEQ ID NO:2. Thus given the limited guidance in combination with the claimed genus, this would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without affecting 90% 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2; (B) the general tolerance of SEQ ID NO:2 to modification and extent of such tolerance given the extent of claimed genus; (C) a rational and predictable scheme for modifying any 3'(2'),5'-bisphosphonate residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

As previously stated, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as the claimed chimeric 3'(2'),5'-bisphosphonates, requires that one of ordinary skill in the art know or be provided with

guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims with such minor structural limitations, clearly it would constitute undue experimentation to arrive at and use the extreme number of encompassed polypeptides. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 90% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required by the breadth of the current claims, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification given the breadth of the claimed genus of chimeric proteins.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the 3'(2'),5'-bisphosphate nucleotidase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those chimeric proteins having the enzymatic

activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising any polypeptide having a one conservative amino acid substitution of SEQ ID NO:2 and retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any chimeric protein having the enzymatic activity of a nucleotidase, comprising polypeptide comprising SEQ ID NO:2 and having one conservative amino acid substitution and retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those chimeric polypeptide methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mondesi Robert can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
8/27/2010

/Richard G Hutson/
Primary Examiner, Art Unit 1652